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Systemic sclerosis prevalence and mortality in Sydney 1974-88

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Abstract

Background: Systemic sclerosis prevalence and mortality estimates have demonstrated wide variability. The sole Australian study published to date demonstrated high prevalence rates when compared to overseas estimates. The prevalence and mortality findings reported in this paper derive from a larger study which addressed the distribution and determinants of systemic sclerosis within Sydney.

Aims: To determine systemic sclerosis prevalence and mortality rates within Sydney over 15 years, 1974-88.

Methods: Cases were ascertained from multiple sources including death certificates, hospitals, physicians, vascular surgeons' and dermatologists' private practices, a systemic sclerosis self-help group and private medical laboratories.

Results: Overall, 715 cases were identified. Females comprised 77% (95%CI:74-80) of cases. Disease of the limited subtype accounted for 79% (95%CI: 76-82) of all systemic sclerosis, being relatively more frequent in living than deceased cases, and in females than males. Crude prevalence estimates appeared to rise between 1975 (4.52/100,000 95%CI:3.75-5.29/100,000) and 1988 (8.62/100,000 95%CI:7.64-9.60/100,000) as did estimates of diffuse disease. However, diffuse disease prevalence, when expressed as a proportion of total disease prevalence, showed no significant temporal change. Although crude mortality rates also showed apparent temporal increases (0.24/100,000 in 1975 to 0.80/100,000 in 1988) standardised mortality rates showed less convincing trends (0.41/100,000 in 1976 and 0.40/100,000 in 1988). Death certificate-derived mortality rates provided relatively large underestimates of total mortality. However, these underestimates were relatively constant over time.

Conclusions: This study has demonstrated systemic sclerosis prevalence and mortality rates comparable to overseas estimates, consistently higher prevalence and mortality rates in females than males, proportionally higher rates of diffuse disease in males than females and in deceased cases than living cases, a diffuse: limited disease ratio apparently

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stable over time, apparently increasing temporal prevalence and mortality rates and, by implication, rising incidence rates. The observed temporal rise in diffuse disease prevalence and the absence of a convincing fall in diffuse disease mortality suggests a rising temporal incidence rate of diffuse disease.

Standardised mortality rates demonstrated less consistent trends than did crude mortality rates and failed to demonstrate convincing declines in mortality subsequent to the introduction of ACE inhibitors for management of systemic sclerosis renal disease. Death certificate-derived systemic sclerosis mortality rates considerably and consistently underestimated systemic sclerosis-all cause mortality. (Aust NZ J Med 1999; 29: 42-50.)

Key words: Systemic sclerosis, scleroderma, epidemiology, prevalence, mortality, death certificates.

TABLE 1
Prevalence, Incidence and Mortality Estimates (/100,000) by District, Country and Year/s of Study

Country and district	Year/s	Prevalence	Incidence	Mortality
USA				
Rochester, Minnesota (1)	1950-79	13.8	1.0	NM
Rochester, Minnesota (2)	1951-67	10.5	1.2	0.6
Baltimore (3)	1949-63	NM	NM	white F=0.22; M=0.13 black F=0.66; M=0.10
US male war veterans (4)	1963-8	0.23	NM	NM
USA (5)	1969-77	NM	NM	white F=0.35; M=0.15 black F=0.63; M=0.31
UK				
West Midlands (6)	1986	3.1	0.4	NM
England & Wales (7)	1968-85	NM	NM	F=0.38; M=0.09
New Zealand				
Auckland (8)	1970-79	6.3	0.63	NM
Denmark (9)	1977-79	6	NM	NM
Germany				
Leipzig (10)	1980-81	10	NM	NM
Australia				
Adelaide	1984-93	20.8	NM	0.21-1.1

NM = no mention

INTRODUCTION

Prevalence, incidence and mortality rates for systemic sclerosis have been previously investigated in the USA,[1-5] England,[6,7] New Zealand,[8] Denmark,[9] and Germany,[10] with marked disparities. Prevalence estimates from various study samples within the USA have ranged from 0.23/100,000[4] to 13.8/100,000.[1] Similar wide-ranging estimates have been made for incidence and mortality rates (Table 1). Estimates of the disease burden within the Australian community were lacking until recently when South Australian 1993 prevalence rates (20.8/100,000) and 1984-93 mortality rates (0.21-1.1/100,000) were published.[11] These may represent underestimates of the true rates but nonetheless remain high when compared to overseas estimates.

This doctoral study, performed between the years 1989 and 1993, investigated the distribution and determinants of systemic sclerosis within Sydney, Australia, for the preceding 15 years – 1974 to 88 inclusive. The study had both descriptive and comparative components, and, for the latter, age-and gender group-matched general practice controls were employed. This article's aim is to describe prevalence and mortality rates within this population. It adds to the latter study[11] by sampling a dissimilar geographical region over a different time frame. It also incorporates the influence of gender and time on these rates. Mortality rates are discussed in terms of total and gender-specific all-cause mortality. Furthermore, an estimate is made of the adequacy of death certificate reporting of this often fatal chronic disease.

MATERIALS AND METHODS

Study data were collected retrospectively between 1989 and 1993.

Case Definition

Identified cases were eligible for the study if they satisfied each of four entry criteria:

1 The patient's diagnosis of systemic sclerosis (scleroderma) was made premortem either before or during the study time frame.

2 The patient's disease satisfied either the American College of Rheumatology Classification (ACR) Criteria[12] or, alternatively, entry criteria specific to this study. The latter comprised one major criterion – sclerodactyly – and at least two of the following minor criteria: Raynaud's phenomenon, oesophageal dysmotility, calcinosis, telangiectasia, or an elevated antinuclear antibody titre. The study-specific criteria were instituted in order to include a subset of CREST syndrome patients who, although manifesting features of systemic involvement (for example sclerodactyly, Raynaud's phenomenon, oesophageal involvement and/or telangiectasia) did not satisfy the ACR classification criteria (ie did not have skin involvement proximal to the metacarpophalangeal joints, digital pitting, finger tapering or bibasilar pulmonary fibrosis).

3 The patient must have resided within Sydney for at least six consecutive months between 1 January 1974 and 31 December 1988.

4 For those systemic sclerosis patients migrating from Sydney within the study time frame, the diagnosis was to have been made prior to emigration.

Specifically excluded were patients with the diagnosis of mixed connective tissue disease or other connective tissue disease (despite prominence of sclerodermatous clinical features), patients with localised scleroderma, porphyria cutanea tarda or scleroedema, or patients whose major reason for migration to Sydney was for further systemic sclerosis management.

Numerator Data: Case Identification

Cases were identified from the following sources in the following chronological order – death certificates, hospital medical records of all public and large private hospitals within Sydney, private practices of physicians, vascular surgeons and dermatologists within Sydney, membership of the Scleroderma Association of NSW, and medical laboratories performing antinuclear antibody estimations. A small number (n=28) were also identified from miscellaneous sources.

Death certification data are recorded by the Registry Office of the state in which the death occurred and provide disease-related data in two parts. Part One data, which record the disease to which death is directly attributed, are computerised and accessible. In contrast, Part Two data, which record other diseases contributing to, but not causing, death, are not computerised and not readily accessible.

Hospital medical records provided identification of all inpatients with a diagnosis of systemic sclerosis, whether or not the admission was related to the disease. This is performed routinely and employs the International Classification of Diseases coding. For the early years of the study prior to computerisation of medical records, this disease index coding employed a manual card indexing system, while for the latter years the disease index recordings were computerised. These hospital medical records did not, however, identify cases treated solely as outpatients. Two Rheumatology department patient databases (Royal North Shore and St George Hospitals) provided identification of all cases treated either as inpatients or outpatients by their departments. The proportion of the latter also identified from the relevant medical records department provided estimates of systemic sclerosis admission rates which were assumed to approximate those in other Sydney hospitals. These systemic sclerosis admission rates were, incidentally, very similar to those from hospitals within Adelaide, South Australia.[11]

Systemic sclerosis patients, ascertained from the private medical practices of physicians, dermatologists and vascular surgeons, were identified by initials, gender and date of birth. However, of 227 identified, 49 could not be reidentified for the purposes of disease validation and subsequent telephone interviews. They were therefore excluded.

Although the local systemic sclerosis self-help group declined to provide a membership list because of confidentiality issues, they mailed invitations of participation on behalf of the study to 168 systemic sclerosis patient members resident within Sydney.

Two of the five largest private medical laboratories performing antinuclear antibody (ANA) screening tests within Sydney allowed access to records of ANA and/or anticentromere antibody-positive patients and the names of the medical practitioners ordering such tests. These records dated retrospectively only as far as 1986. Another two laboratories had destroyed their ANA results for the years relevant to the study. This was the last procedure by which patient identification was sought, was the least thorough method overall, and contributed no further cases.

Systemic sclerosis disease subtype (limited or diffuse), determined by the extent of skin involvement, was ascertained from the patient's medical records.

Denominator Data: Sydney Population and Study Boundary

The Australian Bureau of Statistics provided a series of midyear point estimates of the Sydney population. The 1981 age- and gender-specific population data, comprising the data relevant to the study midpoint, were utilised where relevant.

Sydney was defined along electoral boundaries so that accurate population-based denominator data could be utilised. These comprised the Sydney Statistical Division (SSD) excluding Gosford-Wyong. The north, south, eastern and western boundaries comprised Hawkesbury River, Royal National Park, Pacific Ocean and Nepean River respectively.

Ethical Considerations

Permission to perform this large study was obtained from the Registrar of Births, Deaths and Marriages, the relevant public and private hospital ethics committees, The Scleroderma Association of New South Wales, and the Australian/Australasian Colleges/Faculties of Dermatology, General Practice, Physicians and Surgeons.

Statistics

Although neither prevalence nor mortality are true rates, they are described as such throughout this paper, according to current convention.

Denominator data obtained from the Australian Bureau of Statistics were midyear estimates. Calculated mortality and prevalence rates were also therefore midyear estimates.

All-cause mortality numerator data were obtained from death certificates and other sources (hospitals, nursing homes, medical practitioners, hospital medical records, former friends or relatives). The midyear mortality rates were obtained by adding half the cases dying in a calendar year to half the cases dying in the previous year and expressing these as a proportion of the midyear population.

Similar calculations were performed for prevalence rates, where patients were defined as cases at the time of disease diagnosis. The numerator for the midyear point prevalence was calculated by adding to the previous year's numerator half the incidence numerator and subtracting half the mortality numerator for the calendar year. This was then expressed as a proportion of the midyear population. 1974 rate estimates are artificially low, because 1973 mortality and prevalence data were not sought.

Gender-specific rates were approximated for the years 1975-6, 1978-80, and 1982-4 because gender-specific denominator data for the Sydney population were unavailable. For these years the male and female populations were assumed to equal each other in magnitude.

Indirect standardisation was used to measure standardised mortality rates for 1976, 1986 and 1988 using 1981 calculated age-and gender-specific rates as the standard population.

RESULTS

The study comprises data on 715 cases who fulfilled the study's entry criteria. Excluded were 15 deceased cases and approximately 21 living cases whose disease could not be validated because medical records had either been destroyed or were unavailable; 49 identified through private physician practices but who could not be reidentified for validation purposes; four whose migration to Sydney appeared to be primarily related to systemic sclerosis management; one whose diagnosis was made at postmortem and one who had systemic sclerosis without skin changes (scleroderma sine scleroderma).

The 715 were ascertained from the following sources: death certificates – 92 patients, hospital medical records – 385 patients, rooms of medical specialists – 178 patients (excluding the 49 previously mentioned), Scleroderma Association of NSW – 32 patients, miscellaneous sources – 28 patients, and medical laboratories – no patients.

Adequacy of Numerator Data

The adequacy of case ascertainment was assessed as follows. First, the number and referral pattern of cases were ascertained from 17 of 29 randomly selected primary care medical practitioners. Seven had managed 14 systemic sclerosis patients in total, while ten had managed no such patients. All 14 patients had been referred for shared care either to secondary or tertiary institutions and therefore could be identified by the study's ascertainment methods.

Second, the rate with which cases were only ever managed as hospital outpatients, and therefore not recorded on the medical records disease index, was estimated from the patient-disease data bases from the Rheumatology departments of two large Sydney teaching hospitals. In both instances, the inpatient admission rate for whatever cause following systemic sclerosis diagnosis

TABLE 2
Distribution of 715 Systemic Sclerosis Patients by Gender, Living Status in 1991 and Disease Subtype.

Living status	Female n=555	Male n=160
Living	41 ACR+, diffuse	13 ACR+, diffuse
	229 ACR+, limited	51 ACR+, limited
	5 ACR+, subtype unknown	5 ACR+, subtype unknown
	66 ACR-, limited	6 ACR-, limited
Deceased	45 ACR+, diffuse	30 ACR+, diffuse
	112 ACR+, limited	35 ACR+, limited
	6 ACR+, subtype unknown	4 ACR+, subtype unknown
	31 ACR-, limited	8 ACR-, limited
Unknown	3 ACR+, diffuse	1 ACR+, diffuse
	9 ACR+, limited	4 ACR+, limited
	0 ACR+, subtype unknown	0 ACR+, subtype unknown
	8 ACR-, limited	3 ACR-, limited

ACR+ = satisfies American College of Rheumatology Classification Criteria for Systemic Sclerosis
ACR- = does not satisfy American College of Rheumatology Classification Criteria for Systemic Sclerosis

approximated 50%, similar to that observed from a South Australian prevalence study.[11] Assuming similar patterns in admission rates to other Sydney hospitals, the total number of cases identified from the medical records disease indices of all the Sydney hospitals – 385 – therefore approximated 50% of the total cases having attended Sydney hospitals (n=770).

Third, the proportion of cases having not attended Sydney hospitals after disease diagnosis was assessed by observing the management patterns of cases identified from the Scleroderma Association of NSW membership. Approximately 20% (32/168) had not attended Sydney hospitals, their systemic sclerosis having only ever been treated by specialists in private practice. Again assuming that the management patterns of this membership group were broadly comparable to non-member cases, then the hypothetical total number of cases within Sydney approximated 960. The adequacy of case identification 715 therefore approximated 75% of the hypothetical true number of cases. By virtue of the tracing methodology used, the untraced cases are more likely to have had limited disease, and are also more likely to have lived in the study's early years, when case ascertainment relied largely on death certificate and hospital inpatient data.

Case Distribution by Gender, Living Status and Subtype

The distribution of eligible cases according to gender, living status, disease subtype is shown in Table 2. Cases whose limited systemic disease did not satisfy the ACR preliminary classification criteria approximated 17% of the cohort. The ACR-negative cases with limited disease (n=122) did not differ significantly from the ACR-positive limited disease cases (n=440) with respect to gender, living status or, with the exception of telangiectasia, frequency of system involvement (Table 3). Excluding 20 cases of uncertain disease subtype, the overall limited:diffuse disease subtype ratio was 4.2:1 and was higher in females than in males (ratio in females=5.1:1 and in males=2.4:1). Males more commonly had diffuse disease than did females (OR=2.10; 95%CI=1.35-3.26). This finding remained valid when cases were stratified by living/deceased status (OR=1.64 95% CI=0.78-3.41 and OR=2.22 95%CI=1.20-4.10) respectively.

TABLE 3
Comparison of the Frequency of Disease Characteristics between ACR-positive Cases with Limited Disease, and ACR-negative Cases with Limited Disease

	Odds ratio (95%CI)
Gender	0.63 (0.34-1.14)
Living status	0.46 (0.11-1.64)
Raynaud's phenomenon	0.58 (0.03-4.94)
Telangiectasia	0.59 (0.36-0.97)
Calcinosis	1.26 (0.81-1.96)
Oesophageal involvement	1.06 (0.69-1.64)
Arthralgia/arthritis	1.25 (0.82-1.91)
Myalgia/myositis	1.00 (0.62-1.61)

The ratio of limited: diffuse disease subtype for deceased and living female patients was 3.2:1 and 7.2:1 respectively, and males was 1.4:1 and 4.4:1 respectively, being higher in living patients of either gender (OR=2.26 95%CI=1.38-3.71 and OR=3.06 95%CI=1.34-7.05).

Prevalence

Annual prevalence rates and gender-specific rates are documented in Table 4. Total prevalence rates appeared to rise from 4.52/100,000 (95%CI:3.76-5.28) in 1975 to 8.62/100,000 (95%CI:7.63-9.61/100,000) in 1988. Similar trends were noted for gender-specific rates. Overall, prevalence rates in females were three- to fourfold higher than in males.

The rates of diffuse disease and the percentage with diffuse disease were estimated for alternate years from 1974 to 88 inclusive (Table 5). While the prevalence of diffuse disease also showed an apparent temporal increase, the percentage with diffuse disease showed no significant temporal change (p=0.685).

TABLE 4
Prevalence Estimates 1974-1988 (/100,000) for Total, Female and Male Populations

	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988
Total (+/-95%CI)	4.07 (3.34-4.80)	4.52 (3.75-5.29)	4.62 (3.85-5.39)	5.07 (4.27-5.87)	5.30 (4.48-6.94)	5.68 (4.85-6.53)	6.18 (5.30-7.06)	6.49 (5.59-7.39)	6.78 (5.87-7.69)	7.02 (6.10-7.94)	7.32 (6.38-8.26)	7.60 (6.65-8.55)	8.14 (7.16-9.12)	8.28 (7.02-8.98)	8.62 (7.64-9.60)
Females (+/-95%CI)	6.58 (5.27-7.89)	7.19 (5.82-8.56)	7.53 (6.13-8.93)	7.84 (6.43-9.25)	8.08 (6.65-9.51)	8.74 (7.26-10.22)	9.51 (7.97-11.05)	9.88 (8.33-11.43)	10.56 (8.95-12.17)	10.98 (9.35-12.61)	11.35 (9.70-13.00)	12.00 (10.31-13.69)	12.78 (11.05-14.51)	13.12 (11.38-14.86)	13.76 (12.00-15.52)
Males (+/-95%CI)	1.56 (0.96-2.26)	1.86 (1.17-2.59)	1.96 (1.22-2.72)	2.31 (1.55-3.11)	2.52 (1.73-3.35)	2.63 (1.82-3.46)	2.84 (2.01-3.71)	3.02 (2.16-3.92)	2.99 (2.14-3.86)	3.06 (2.20-3.94)	3.28 (2.40-4.20)	3.46 (2.56-4.40)	3.44 (2.55-4.37)	3.39 (2.51-4.31)	3.42 (2.54-4.26)

Mortality

One hundred and seven deceased cases were identified from Part One data and a further one case from Part Two data after an audit of 10,000 randomly selected death certificates. Of the 107 deceased cases identified from Part One data, 92 satisfied all four study entry criteria. Of the 15 ineligible patients, six did not meet the four entry criteria, six had destroyed medical records which allowed neither disease nor residential validation, and three had medical records which were insufficiently detailed to allow full validation.

Crude total and gender-specific mortality rates, crude mortality rates derived solely from death certification data, and standardised mortality rates for the years 1976, 1986 and 1988 are recorded in Table 6. Crude total, female-specific mortality rates, and death certificate-derived total mortality rates showed apparently increasing rates. Male-specific crude mortality rates and death certificate-derived crude mortality rates for diffuse disease (Table 7) showed less convincing trends. Adjusted total-, female-and male-specific mortality rates, mortality rates from diffuse disease and mortality rates from diffuse disease expressed as a proportion of total deaths failed to demonstrate a consistently changing trend over time (Table 7). Female-specific rates again consistently exceeded male rates, although not to the same magnitude as those observed for prevalence estimates.

All-cause mortality rates were compared to mortality rates derived solely from death certificates. Of 199 cases who died within NSW between 1974 and 1988, 92 (46.2%) were identified from Death Certificate Part One data, the latter representing the number of cases interpreted as dying from the disease. The remainder represented those whose death was considered unrelated to systemic sclerosis. Of the deceased cases, the proportion whose death was reported in Part One of the death certificate remained relatively constant between 1974 and 1988. Systemic sclerosis underreported in Part One of the death certificates of patients with diffuse disease.

DISCUSSION

The Sydney Scleroderma Epidemiology Study, comprising data on 715 cases, is second only in size to one of 727 systemic sclerosis patients from a tertiary referral centre in the USA.[13] It is, however, the largest population-based systemic sclerosis study to date.

The magnitude of this study and its subsequent conclusions partly depend on decisions which relate to case definition. A premortem diagnosis was made in order to define similar eligibility criteria for controls and cases. (Thus one potential case was excluded.) Eligibility also included those whose disease characteristics satisfied the ACR classification criteria for systemic sclerosis,[12] or

TABLE 5
Prevalence of Diffuse Disease (/100,000), 1974-88

	1974	1976	1978	1980	1982	1984	1986	1988
Total diffuse disease	0.86 (0.52-1.20)	0.93 (0.59-1.27)	1.31 (0.91-1.72)	1.34 (0.93-1.75)	1.78 (1.31-2.25)	1.72 (1.27-2.18)	1.76 (1.31-2.21)	1.85 (1.39-2.31)
Percentage with diffuse disease	21.1 (13.8-28.4)	19.9 (13.3-26.5)	24.5 (17.9-31.1)	21.6 (15.8-27.4)	26.2 (20.3-32.1)	23.4 (18.0-28.8)	21.5 (16.6-26.4)	21.6 (16.8-26.3)

TABLE 6
Sydney Scleroderma Mortality Estimates (/100,000) 1974-88

	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988
Total, crude, all-cause (*) (10^{-5})	0.10 (0.0 0.22)	0.24 (0.06- 0.42)	0.33 (0.12- 0.54)	0.30 (0.11- 0.49)	0.31 (0.11- 0.51)	0.36 (0.15- 0.57)	0.32 (0.12 -0.52)	0.39 (0.17- 0.61)	0.48 (0.24- 0.72)	0.55 (0.29- 0.81)	0.52 (0.48- 1.04)	0.65 (0.37 0.93)	0.81 (0.50- 1.12)	0.74 (0.45- 1.03)	0.80 (0.50- 1.10)
Female-specific mortality	0.07 (0.00- 0.83)	0.27 (0.14- 0.40)	0.54 (0.38- 0.71)	0.49 (0.27- 0.71)	0.43 (0.23 0.63)	0.42 (0.24- 0.60)	0.42 (0.24- 0.60)	0.54 (0.26- 0.82)	0.64 (0.36- 0.92)	0.66 (0.38- 0.94)	0.69 (0.42- 0.96)	0.90 (0.60- 1.20)	1.09 (0.74- 1.44)	1.11 (0.77- 1.45)	1.18 (0.83- 1.53)
Male-specific mortality	0.14 (0.00- 0.33)	0.20 (0.00- 0.50)	0.14 (0.00- 0.33)	0.10 (0.00- 0.26)	0.20 (0.00- 0.42)	0.29 (0.02- 0.56)	0.23 (0.00- 0.47)	0.23 (0.00- 0.47)	0.32 (0.04- 0 60)	0.44 (0.11 0.77)	0.34 (0.05- 0.63)	0.40 (0.09- 0.71)	0.52 (0.17- 0.87)	0.36 (0.07- 0.65)	0.42 (0.11- 0.73)
Crude, death certificate data only	0 07 (0 00- 0.16)		0.05 (0.00 0.13)		0.13 (0.00- 0.26)		0.14 (0.01- 0.28)		0.21 (0.05- 0.37)		0.28 (0.10- 0.47)		0.32 (0.13- 0.52)		0.34 (0.14- 0 54)

*Adjusted rates were ascertained using indirect standardisation by applying the 1981 age and gender-specific mortality rates to age- and gender specific components of the 1976, 1986 and 1988 Sydney population. The total, female-specific and male specific rates for 1976 were 0.41 (0.18-0.64), 0.47 (0.14-0.79) and 0.24 (0.00-0.58) respectively; the 1986 rates were 0.51 (0.31-0.70), 0.86 (0.46-1.26) and 0.71 (0.14-1.27) respectively; the 1988 rates were 0.40 (0.25-0.55), 0.91 (0.51 1 30) and 0.81 (0.21-1.40) respectively.
The 1981 Sydney population (n=3112750) was distributed in percentage terms by age (in decades) and gender (F:M) as follows: 0-9 yrs=6.9 and 7.2; 10-19 yrs 7 4 and 7.7; 20 29 8.0 and 8.0; 30-39 yrs 7.0 and 7.2; 40-49 yrs 4.9 and 5.2; 50-59 yrs 4.9 and 4.9; 60-69 yrs 3.8 and 3.3; 70 79 yrs 2.4 and 1.6; 80-89 yrs 1.0 and 0.4; and 90-99 yrs 0.2 and 0.0 respectively.

local study-specific criteria. The latter patients, representing 17% of the cohort, had features of sclerodactyly and involvement of at least one other organ system and comprised a subset of those with limited disease. The current ineligibility of this patient group for the ACR classification criteria highlights an inadequacy of the latter which, in its design, demonstrated a selection bias towards those with diffuse disease. A six month consecutive residence within Sydney was instituted in order to exclude systemic sclerosis cases who recurrently visited Sydney for purposes of disease management. Eligibility of cases migrating from Sydney depended on a diagnosis being made prior to emigration for logistic reasons.

Case ascertainment was incomplete, although multiple sourcing was utilised. Estimates were made of the magnitude of the case ascertainment – approximating 75% being positively identified – using a method devised specifically for the study. Capture-recapture methods[14] were not utilised because the latter methodology had not been widely applied to human epidemiology when case ascertainment began and the degree of overlap between different case ascertainment sources was not easily retrieved.

One source of case underascertainment was the group of Sydney cases whose disease was diagnosed only after migration from Sydney. The consequences of such migration bias are such to underestimate any measures of causation linked directly or indirectly to residential status and would be more likely of environmental than genetic aetiology. A second source of case under-ascertainment related to the inadequacy of initial patient identification by initials, gender and date of birth, a strategy advised by ethical committees to protect patient confidentiality. Although useful

TABLE 7
Mortality Rates of Diffuse Disease (/100,000) 1974-88

	1976	1978	1980	1982	1984	1986	1988
Total	0.17 (0.03- 0.32)	0 16 (0.02- 0 30)	0.10 (0.00 0.21)	0.13 (0.01- 0.25)	0.13 (0.01- 0.25)	0.12 (0.00- 0.24)	0.21 (0.06- 0.36)
Percentage with diffuse disease	50 (19-81)	50 (19-81)	33 (2-64)	33 (6-60)	29 (5-53)	16 (2 30)	25 (9-41)
Crude mortality rates, death certification only	0.03 (0.024- 0.036)	0.03 (0.024- 0.036)	0.00	0.06 (0.052- 0.068)	0.00	0.09 (0.082- 0.098)	0.09 (0.080- 0. 100)

theoretically, it was much less useful in practice because complete patient data (especially date of birth) were frequently not provided by physicians. This led to an excess of 20% underascertainment of potential cases thus identified. For the purposes of epidemiological research therefore this large problem supports an argument for case identification using cases' full names. A third potential source of case underascertainment was time-dependent. Early within the study time-frame the source of case ascertainment was largely from hospital medical records (inpatient cases) and death certificates, whereas later in the study time-frame other sources of case ascertainment were added, including physician private practices and the scleroderma self-help group. A fourth potential source of case underascertainment comprised an hypothetical group of cases only ever managed by their general medical practitioner. This group would most likely have mild disease. Although the magnitude could not be ascertained with any certainty, estimates were made by sampling the referral patterns of general medical practitioners from whom controls were ascertained. All had referred their cases on to secondary or tertiary levels of referral from which they could be detected by the study's case ascertainment methods. If the referral patterns of these randomly sampled general medical practitioners were representative of the non-sampled practitioners, then the size of this fourth group of undetected cases would unlikely be large. Fifth and finally was a group with undiagnosed systemic sclerosis. However, the eligibility or otherwise of these cases depends on case definition – specifically whether date of symptom onset or date of diagnosis determines the transition from control (non-case) to case. This remains an unresolved issue with a disease of such variable onset as systemic sclerosis, where the onset of first and second disease symptoms may predate diagnosis often by decades (unpublished data from current study).

The limited disease subtype accounted for approximately 80% of all disease subtypes, representing a higher proportion of all systemic sclerosis cases than previously described.[15] This could partly be explained, however, by inclusion in our study of the ACR-negative limited disease group. The more aggressive diffuse disease subtype occurred more commonly in males, the latter gender comprising approximately one quarter of all cases. These features are also characteristic of rheumatoid arthritis.

Total and female-specific prevalence rates and crude mortality rates appeared to rise between 1974 and 1988, indicating indirectly that incidence must also have apparently risen disproportionate to mortality. These findings are consistent with those of the only other study which investigated temporal disease trends.[16] Whether or not these apparently rising rates represent true increases, apparent increases explained on the basis of greater disease recognition with time and/or temporally-dependent methods of case ascertainment, or an admixture of the two, remains unresolved. One argument supporting a truly increasing prevalence relates to the apparent temporally increasing prevalence of diffuse disease. This argument depends on two assumptions – that physicians maintained a relatively constant ability to diagnose diffuse disease over the study interval, and that hospital admission rates (and hence case identification) for diffuse disease were also relatively constant over the study interval. An argument against a truly increasing prevalence rate pertains to the temporal distribution of the hypothetical number of untraced cases. As alluded to previously, these patients were more likely to have clustered around the early years of the study, where case ascertainment was less complete.

An apparent temporal rise in diffuse disease prevalence between 1974 and 1988 in the absence of a rise in diffuse disease mortality suggests that diffuse disease incidence rose over this time.

It is interesting that the proportion with diffuse disease remained relatively constant over time. While this finding should be regarded with some caution, taking into account the relatively short interval over which the study took place, the possibility of time-dependent case underascertainment and the relatively wide confidence intervals of the proportions, the finding may shed some light on the immunogenetic aspects of systemic sclerosis.

Although crude and female-specific mortality rates appeared to rise over 15 years, with female rates slightly but consistently exceeding male rates, this trend was less marked when the data were age standardised. No reduction in mortality rate was observed despite the implementation of ACE-inhibitors for the management of systemic sclerosis-related hypertension over the study interval. As estimated from death certification data, mortality rates from systemic sclerosis were underestimated, only reporting 46% of total systemic sclerosis deaths. Death certificate-derived mortality rates from systemic sclerosis, expressed as a proportion of all-cause mortality

rates, were also relatively constant over the study time frame, accounting for slightly less than 50% of all such deaths. Therefore, although death certification-derived systemic sclerosis mortality considerably underestimated systemic sclerosis all-cause mortality rates, the former reliably demonstrated temporal trends in systemic sclerosis all-cause mortality. Whether this finding translates to other time frames and other geographical locations remains undetermined, but currently supports the justification for a systemic sclerosis mortality study based on death certification data when investigating temporal trends.[9] Perhaps a little surprisingly, systemic sclerosis was underrecorded in the Death Certificate Part One data in patients with diffuse disease.

This study uses standardisation procedures for comparison of rates and is the largest population-based study of systemic sclerosis. The careful adherence to study base criteria meant that this study does not suffer from referral bias, and the possible attendant biases in terms of disease activity/severity or socioeconomic influences on referral bias. It has demonstrated systemic sclerosis prevalence and mortality rates comparable to overseas estimates, consistently higher prevalence and mortality rates in females than males (in accordance with the 3:1 female preponderance of the disease), proportionally higher frequencies of diffuse disease in males than females, an apparent temporal rise in diffuse disease prevalence in the absence of a rise in diffuse disease mortality suggesting a rising diffuse disease incidence rate, an apparently temporally stable diffuse: limited disease ratio and apparently increasing temporal prevalence and mortality rates. Although a truly increasing prevalence cannot be excluded, the apparently increasing prevalence may purely reflect temporal differences in case ascertainment. We have supported the use of patients' full names rather than initials for the purposes of epidemiological research. We have also argued for modification of the currently used ACR classification criteria for systemic sclerosis to include a subset of patients with limited systemic disease, whose disease characteristics fall outside the previously mentioned classification criteria. Finally we have shown that the death-certificate-derived systemic sclerosis mortality rates considerably underestimated systemic sclerosis mortality from any cause, but that the underestimate was relatively constant with time and therefore reliably reflected temporal trends in systemic sclerosis all-cause mortality rates. ■

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